ehp ENVIRONMENTAL HEALTH PERSPECTIVES
http://www.ehponline.org

Outdoor Particulate Matter Exposure and Lung Cancer: A Systematic Review and Meta-Analysis

Ghassan B. Hamra, Neela Guha, Aaron Cohen, Francine Laden, Ole Raaschou-Nielsen, Jonathan M. Samet, Paolo Vineis, Francesco Forastiere, Paulo Saldiva, Takashi Yorifuji, and Dana Loomis

http://dx.doi.org/10.1289/ehp.1408092
Received: 6 January 2014
Accepted: 3 June 2014
Advance Publication: 6 June 2014

NIH National Institute of Environmental Health Sciences

Outdoor Particulate Matter Exposure and Lung Cancer: A Systematic Review and Meta-Analysis

Ghassan B. Hamra,[1] Neela Guha,[1] Aaron Cohen,[2] Francine Laden,[3,4] Ole Raaschou-Nielsen,[5] Jonathan M. Samet,[6] Paolo Vineis,[7] Francesco Forastiere,[8] Paulo Saldiva,[9] Takashi Yorifuji,[10] and Dana Loomis[1]

[1]International Agency for Research on Cancer, Lyon, France; [2]Health Effects Institute. Boston, Massachusetts, USA; [3]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA; [4]Departments of Environmental Health and Epidemiology, Harvard School of Public Health. Boston, Massachusetts, USA; [5]Institute of Cancer Epidemiology, Danish Cancer Society, Copenhagen, Denmark; [6]Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, California, USA; [7]Department of Epidemiology and Public Health, Imperial College London, London, United Kingdom; [8]Department of Epidemiology, Regional Health Authority, Lazio, Roma, Italy; [9]Department of Pathology, School of Medicine, University of São Paulo, São Paulo, Brazil; [10]Department of Human Ecology, Graduate School of Environmental and Life Sciences, Okayama University, Okayama, Japan

Address correspondence to Ghassan Hamra, Section of Environment and Radiation, International Agency for Research on Cancer, 150 Cours Albert Thomas, 69006 Lyon, France. Telephone: +33 4 72 73 89 12. E-mail: hamrag@fellows.iarc.fr

Running head: Air pollution and lung cancer risk

Acknowledgments: The work reported in this paper was undertaken during the tenure of a postdoctoral fellowship awarded to Ghassan B. Hamra by the International Agency for Research on Cancer. Aaron Cohen is employed by the Health Effects Institute, Boston, MA, USA; the views expressed in this article do not necessarily represent those of Health Effects Institute or its sponsors.

Disclaimer: The views expressed in this article do not necessarily represent those of the Health Effects Institute (HEI) or its sponsors.

Competing financial interests: We have no competing financial interests to declare.

Abstract

Background: Particulate matter (PM) in outdoor air pollution was recently designated a Group I carcinogen by the International Agency for Research on Cancer (IARC). This determination was based on the evidence regarding the relationship of $PM_{2.5}$ and PM_{10} to lung cancer risk; however, the IARC evaluation did not include a quantitative summary of the evidence.

Objective: To provide a systematic review and quantitative summary of the evidence regarding the relationship between PM and lung cancer.

Methods: We conducted meta-analyses of studies examining the relationship of exposure to $PM_{2.5}$ and PM_{10} with lung cancer incidence and mortality. In total, 18 studies met inclusion criteria and provided the information necessary to estimate the change in lung cancer risk per 10-$\mu g/m^3$ increase in exposure to PM. We used random effects analyses to allow between study variability to contribute to meta-estimates.

Results: The meta-relative risk (95% CI) for lung cancer associated with $PM_{2.5}$ was 1.09 (95% CI: 1.04, 1.14). The meta-relative risk of lung cancer associated with PM_{10} was similar, but less precise: 1.08 (95% CI: 1.00, 1.17). Estimates were robust to restriction to studies that considered potential confounders, as well as sub-analyses by exposure assessment method. Analyses by smoking status showed that lung cancer risk associated with $PM_{2.5}$ was greatest for former smokers, 1.44 (95% CI: 1.04, 1.22) followed by never smokers, 1.18 (95% CI: 1.00, 1.39), and then current smokers, 1.06 (95% CI: 0.97, 1.15). In addition, meta-estimates for adenocarcinoma associated with $PM_{2.5}$ and PM_{10} were 1.40 (95% CI: 1.07, 1.83) and 1.29 (95% CI: 1.02, 1.63), respectively.

Conclusion: The results of these analyses, and the decision of the IARC working group to classify PM and outdoor air pollution as carcinogenic (Group 1), further justify efforts to reduce exposures to air pollutants that can arise from many sources.

Introduction

The complex mixture of outdoor air pollution contains a number of known carcinogens and has been associated with increased lung cancer risk in many studies over the past 50 years. Past reviews of the body of evidence regarding outdoor and household air pollution indicated that both were associated with lung cancer risk; specifically, exposures to increased levels of particles, as well as other indices of air pollution, were associated with increased lung cancer risk. However, the evidence was considered inconclusive regarding which specific components of the air pollution mixture are driving the increased risk (Samet and Cohen 2006). The International Agency for Research on Cancer (IARC) recently concluded that exposure to outdoor air pollution and to particulate matter in outdoor air (PM) are carcinogenic to humans (IARC Group 1) and cause lung cancer (IARC, in press; Loomis et al. 2013). Epidemiological studies of long-term residential exposure to outdoor air pollution in terms of PM played a critical role in IARC's evaluation.

In this manuscript, which originated with the IARC review, we provide meta-analyses of lung cancer risk associated with exposure to particulate matter in outdoor air, specifically $PM_{2.5}$ (particles with aerodynamic diameter less than 2.5 microns, or fine particles) and PM_{10} (particles with aerodynamic diameter less than 10 microns, or inhalable particles). We performed analyses in subgroups defined by geographic region, potential confounders and effect modifiers, and exposure assessment method. We also examined the influence of single studies to the overall meta-estimate.

Methods

Literature search

The studies included in this analysis were a key component of the epidemiological evidence reviewed by the IARC working group in its evaluation of the carcinogenicity of PM, as reported in IARC Monograph 109 (IARC, in press; Loomis et al. 2013). Relevant studies were identified in several stages, beginning with a systematic search of the PubMed database using the keywords air pollution, particulate matter, or traffic and cancer [air pollution OR particulate matter OR traffic AND cancer] in the title or abstract, with the results restricted to studies of humans. An initial search was conducted in December, 2012 and updated automatically through October 2013. This search retrieved 604 studies.

Abstracts of the papers retrieved in the electronic search were screened manually for relevance to the topic of the IARC Monograph on outdoor air pollution. Ecological studies, with data on both outcome and exposure collected at the aggregate level, were excluded because of the inherent limitations of such studies. Instead, we considered all cohort and case control studies available, which provide individual outcome information and, in many cases, individual measures of exposure. The reference lists of the papers judged to be relevant at this stage were then searched for other potentially relevant papers, which were screened in turn. Members of the Working Group who were familiar with the research identified 3 additional studies that were in press at the time of the electronic search. Through this process, 201 potentially relevant papers were identified. Electronic full-text copies of those papers were made available to members of the Working Group, who reviewed the search results and the papers in detail and selected those studies considered relevant for inclusion in the Monograph.

Inclusion and exclusion criteria

Studies were included in the current meta-analysis if they provided quantitative estimates of residential exposure to $PM_{2.5}$ and/or PM_{10}. Further, studies were required to provide quantitative estimates of the change in lung cancer incidence or mortality associated with exposure to either indicator of PM; this could be reported as the change in risk per $\mu g/m^3$ or quantile of exposure. Studies that reported results for the association of lung cancer with other air pollutants or exposure to traffic, but did not provide quantitative estimates for PM were not included in the meta-analysis.

We considered lung cancer mortality and incidence studies together, as mortality is a valid indicator of incidence. Survival rates provided by the Surveillance, Epidemiology, and End Results (SEER) program from 2003-2009 estimate 5-year survival rates among US white males and females at 14.5% and 19.5%, respectively (Howlader et al. 2013). Since the case-fatality rate is high for lung cancer, mortality and incidence are comparable and it is, thus, reasonable to include both outcomes within the same meta-analysis.

Where multiple publications included overlapping study populations, we included the publication that considered the largest number of cases and/or with results based on the longest follow-up. In addition, we did not have any restrictions based on whether or not a study adjusted for specific confounders. All studies adjusted for the effect of age and gender; however, the sets of other potential confounders for which adjustments were made varied by each study. Thus, the sensitivity of estimates to confounder adjustment was considered. All risk estimates were abstracted by one author, reviewed by the IARC Working Group, and double checked for accuracy by a second author.

Statistical analyses

All study estimates were converted to represent the change in lung cancer risk per 10 $\mu g/m^3$ unit increase in exposure to $PM_{2.5}$ or PM_{10}. If we could not reliably convert the values in a particular study to the aforementioned units, the authors of the original study were contacted for further information. If information necessary to convert estimates could not be obtained, the study was excluded from consideration.

Estimates from the studies were combined using a random effects model, which allows between study heterogeneity to contribute to the variance (DerSimonian and Laird 1986). I^2 values are reported, which represent the estimated percent of the total variance that is explained by between study heterogeneity (Higgins et al. 2003). We also conduct chi-square tests of homogeneity to compare meta-estimates divided into subgroups by region, smoking status, and exposure assessment method. In some cases, individual studies reported results only for subgroups, such as by sex or time period of study. Such stratified estimates were first combined into a single, study-specific estimate using fixed effects regression and then included in analyses to obtain the overall meta-estimate. In addition, studies restricted to certain subgroups were considered to have adjusted for confounding by the subgroup of interest; for example, studies among men only were considered to have accounted for the confounding effects of sex. Finally, forest and funnel plots were created to provide a visual summary of the distribution of study specific effect estimates. In lieu of statistical tests of funnel plot asymmetry, we conducted trim and fill analyses. The trim and fill analyses remove the smallest studies until a symmetric funnel plot is obtained; then, those studies removed are added back with their hypothetical 'counterparts' to recalculate the meta-estimate that would have been obtained from a symmetric funnel plot (Duval and Tweedie

2000; Higgins et al. 2008). Analyses were conducted using the STATA (v12.1, College Station, Texas, USA).

Results

Studies included

We identified 17 cohort studies (Beelen et al. 2008; Beeson et al. 1998; Cao et al. 2011; Carey et al. 2013; Cesaroni et al. 2013; Hales et al. 2012; Hart et al. 2011; Heinrich et al. 2013; Jerrett et al. 2013; Katanoda et al. 2011; Krewski D 2009; Lepeule et al. 2012; Lipsett et al. 2011; McDonnell et al. 2000; Naess et al. 2007; Pope et al. 2002; Raaschou-Nielsen et al. 2013) and one case-control (Hystad et al. 2013) study of lung cancer that provided estimates of the quantitative relationships between the risk of lung cancer and exposure to $PM_{2.5}$ or PM_{10} that could be expressed per 10μg/m^3 change in PM. Estimates from one cohort study (Naess et al. 2007) could not be converted to units of 10μg/m^3 and, thus, this study did not contribute to the meta-estimates. Additionally, a recently accepted paper (Puett et al., in press) was included in this analysis because it met the criteria for inclusion.

Table 1 summarizes the 18 studies included in these analyses. In total, there were 14 and 9 studies that provided estimates of the lung cancer risk associated with exposure to $PM_{2.5}$ and to PM_{10}, respectively. There were four studies from Europe, eight studies from North America and two studies from other regions that contributed to the overall meta-estimates for $PM_{2.5}$. Regarding PM_{10}, there were three European studies, five North American studies, and one study from another region that contributed to the overall meta-estimates.

We note that Jerrett et al. (2013) is a subset of the full ACS-CPS II cohort considered in Krewski et al. (2009). Jerrett et al. (2013) use land use regression to estimate PM, whereas Krewski et al.

(2009) used fixed site monitors; additionally, each study considers different confounders in final analyses. Thus, we exclude Jerrett et al. (2013) from all analyses where it would overlap with Krewski et al. (2009).

Overall meta-estimates for $PM_{2.5}$ and PM_{10}

Figure 1 presents the estimated effect for each study, grouped by the continent where the study was conducted; Jerrett et al. (2013) is included in Figure 1 for visualization, but does not contribute overall or continent specific meta-estimates. All estimates represent the change in the risk of lung cancer mortality/incidence associated with a $10\mu g/m^3$ increase in $PM_{2.5}$ or PM_{10}. The meta-relative risk (95%CI) for lung cancer associated with $PM_{2.5}$ was 1.09 (95% CI: 1.04, 1.14). The meta-relative risk of lung cancer associated with PM_{10} was similar, but less precise: 1.08 (95% CI: 1.00, 1.17). When restricting to cohort studies that examine both measures of PM (AHSMOG, ACS-CPS-II, TrIPS, CTS, NHS, Clinical Practice Research Datalink, and ESCAPE), the meta-estimates associated with $PM_{2.5}$ and PM_{10} are 1.09 (95% CI: 1.06, 1.13) and 1.07 (95% CI: 0.98, 1.15), respectively. Random effects estimation for these values may suggest inconsistencies between studies. The between study variance for $PM_{2.5}$ and PM_{10} were 56.4% and 74.6% of the total variance, respectively. Chi-square tests of homogeneity provided little evidence of difference between continent specific meta-estimates for $PM_{2.5}$ ($p=0.656$), and modest evidence of heterogeneity by continent specific meta-estimates for PM_{10} ($p=0.074$).

Funnel plots for both $PM_{2.5}$ and PM_{10} were visually asymmetrical (see Supplemental Material, Figure S1); thus, trim and fill analyses were conducted to test the volume of information that would be necessary to construct a symmetrical funnel plot. With respect to $PM_{2.5}$, the estimate accounting for funnel plot asymmetry was 1.08 (95% CI: 1.03, 1.13); this estimate required

trimming and filling in the funnel plot with three hypothetical studies. With regards to PM_{10}, the estimate accounting for funnel plot asymmetry was 1.00 (95% CI: 0.92, 1.08); this estimate required filling in the funnel plot with four hypothetical studies. Additionally, we conducted influence analyses to determine if any specific study highly influenced the overall meta-estimate. Results showed that overall meta-estimates were not reliant on inclusion of any specific study; confidence intervals for meta-estimates excluding one study at a time were overlapping, and meta-estimates consistently supported a positive association between PM exposure and lung cancer incidence and mortality (see Supplemental Material, Table S1).

Subgroup analyses

Table 2 presents subgroup analyses by continent, exposure assessment method, and smoking status; in addition, meta-estimates excluding studies that did not adjust for confounders of interest are presented. Region specific meta-estimates are also summarized, with individual study estimates, in Figure 1. The $PM_{2.5}$ meta-estimates for Europe, North America, and other continents were 1.03 (95% CI: 0.89, 1.20), 1.11 (95% CI: 1.05, 1.16), and 1.13 (95% CI: 0.94, 1.34), respectively (Figure 1a). While these estimates show a slight variation, their confidence intervals are largely overlapping, and homogeneity tests suggest no evidence of differences across regions. Regarding PM_{10}, the meta-estimates for Europe and North America are 1.27 (95% CI: 0.96, 1.68), and 1.02 (95% CI: 0.96, 1.09), respectively (Figure 1b). The estimate from North America, based on five studies, was more precise and less suggestive of a relationship between PM_{10} and lung cancer risk. A study in New Zealand (Hales et al., 2012) was the only one available outside of Europe and North America; the reported estimate from this study was 1.16 (95% CI: 1.04, 1.29). Estimates by continent do not appear heterogeneous (Table 2).

With regard to exposure assessment method, meta-estimates from studies using fixed site monitors were compared to those from studies using modelling based estimation techniques, e.g. land-use regression. For both $PM_{2.5}$ and PM_{10} exposure, the meta-estimate from studies using fixed site monitors was higher than the meta-estimate from studies using modelling based exposure assessment techniques. However, homogeneity tests for $PM_{2.5}$ and PM_{10} ($p = 0.268$ and $p = 0.484$, respectively) suggest no difference between exposure assessment method subgroups (Table 2).

We also conducted analyses by subgroups of current, former, and never smokers. The meta-estimate for lung cancer risk associated with $PM_{2.5}$ was greatest for former smokers, 1.44 (95% CI: 1.04, 2.01) followed by never smokers, 1.18 (95% CI: 1.00, 1.39), and then current smokers, 1.06 (95% CI: 0.97, 1.15). A test of homogeneity suggests no evidence of differences between subgroups ($p = 0.197$); a lack of statistical power to detect differences may have contributed to this finding. The meta-estimate for lung cancer risk associated with PM_{10} for never smokers was 1.11 (95% CI: 0.94, 1.33). Estimates for current and former smokers were only available from one study (Raaschou-Nielsen et al. 2013), and were 1.27 (95% CI: 1.02, 1.58) and 0.98 (95% CI: 0.67, 1.44), respectively.

Table 2 summarizes meta-estimates by subgroups of studies that account for confounding by smoking status, SES/income, education, and occupation (which includes occupational exposure). The magnitude of the meta-estimates of lung cancer risk associated with $PM_{2.5}$ varied modestly but remained elevated with various adjustments. The meta-estimates of lung cancer risk associated with PM_{10} exposure behaved similarly, but there was some indication of greater sensitivity to the control of covariates, particularly occupation.

Histologic subtypes

Table 3 provides estimates of the relationship between $PM_{2.5}$ and PM_{10} and the two most frequent histological subtypes of lung cancer: adenocarcinoma and squamous cell carcinoma. The meta-estimates for adenocarcinoma associated with $PM_{2.5}$ and PM_{10} were 1.40 (95% CI: 1.07, 1.83) and 1.29 (95% CI: 1.02, 1.63), respectively. The meta-estimate of the relationship between squamous cell carcinoma and $PM_{2.5}$ is 1.11 (95% CI: 0.72, 1.72). The relationship between PM_{10} and squamous cell carcinoma was examined in only one study (Raaschou-Nielsen et al. 2013) in our review, which reported a RR of 0.84 (95% CI: 0.50, 1.41) per 10 $\mu g/m^3$.

Discussion

We conducted meta-analyses of the relationship between exposure to ambient PM and lung cancer incidence and mortality. Meta-estimates combine incidence and mortality studies due to the high fatality rate among incident lung cancers. These quantitative analyses complement the qualitative classification of the evidence by the Monograph 109 working group (IARC, in press). Most of the data were obtained from cohort studies, and our analytical results are similar across diverse study populations, potential confounders considered, as well as exposure assessment methods; this consistency supports the IARC Working Group's conclusion that PM from outdoor air pollution is a Group 1 carcinogen and causes lung cancer. Air pollution is ubiquitous, and all populations are exposed to it at some level, albeit with considerable variation between the most and the least polluted areas (Brauer et al. 2012). Thus, these results are important for policy makers and public health practitioners across the world.

In this analysis, we focused attention on $PM_{2.5}$ and PM_{10}, which are prominent components of the ambient air pollution mixture. Of course, PM_{10} includes the $PM_{2.5}$ size fraction; however, these particle size groups are believed to differ in regards to human health effects. $PM_{2.5}$ includes

a higher proportion of mutagenic species (Buschini et al. 2001; Valavanidis et al. 2008), many of which are products of combustion (Brauer et al. 2001). Further, smaller particles penetrate more deeply into the lung and are more likely to be retained (Stuart 1976). On the other hand, the coarse fraction of the PM_{10} size group consists mainly of minerals and biologic materials (Valavanidis et al. 2008). Thus, $PM_{2.5}$ is generally believed to be most relevant to health effects, including cancer.

A number of potential confounders are often considered when examining the relationship between PM and lung cancer risk, the most important overall being tobacco smoking. Meta-estimates for the relationship of $PM_{2.5}$ to lung cancer were consistent with the overall meta-estimate when restricting to studies that considered confounding by smoking status, SES/income, education, occupation, or sex. In addition, analyses by continent of study (Europe, North America, or other) yielded consistent, positive associations between $PM_{2.5}$ and lung cancer. For PM_{10}, the data were less abundant and the findings of sensitivity analyses were less robust than for $PM_{2.5}$.

We did not conduct statistical tests for assessment of publication bias, because these tests are specific to randomised controlled trials (Sterne et al. 2011) and rely on assumptions that are not applicable to meta-analyses of observational research (Egger et al. 1998). Trim and fill analyses were conducted, which require a strong assumption that a funnel plot should be symmetrical and that there is no between study variance (Duval and Tweedie 2000; Higgins et al. 2008). Conclusions regarding the relationship between $PM_{2.5}$ and lung cancer risk were robust. Trim and fill analyses for PM_{10} and lung cancer risk led to a null-centered estimate; however, this required trimming and filling four out of 10 studies. In short, a large number of hypothetical studies would be required to construct a symmetrical funnel plot and change the results of our

meta-analyses. In addition, results for lung cancer risk from $PM_{2.5}$ and PM_{10} were robust to influence analyses, where the meta-estimate was recalculated with the systematic exclusion of each study.

Exposure assessment techniques differed across studies. Some studies used fixed site monitors, while others employed more complex modelling approaches; regardless of the method used, all individuals in a study are assigned an estimate of individual level exposure. Modelling techniques, such as land use regression and air dispersion, attempt to provide residential estimates of exposure to PM, while fixed site monitors indicate group level exposures without further modelling. In fact, none of the exposure assessment methods used provide a true, individual level measure of exposure to PM. Meta-estimates of lung cancer risk associated with both $PM_{2.5}$ and PM_{10} from studies using fixed site monitors were slightly higher than those obtained from studies using advanced exposure modelling methods. However, homogeneity tests suggest no difference in estimates between exposure assessment techniques.

In addition to adjusting for smoking status, some studies provided analyses for $PM_{2.5}$ by smoking subgroups allowing assessment differential effects of PM by smoking status (never, former, and current). Data were limited for examining the relationship between PM_{10} and lung cancer risk; only three studies provided any subgroup specific information, which pertains only to never smokers. Six studies provide information on the relationship between $PM_{2.5}$ and lung cancer by never, former, or current smoking status, and one presented results specific to never smokers. Meta-estimates from these studies suggest that never and former smokers may have elevated risk of lung-cancer associated with $PM_{2.5}$ compared to current smokers; however, even current smokers exhibited a modest, but imprecise, elevated risk of lung cancer due to $PM_{2.5}$. Further, these results are limited by lack of detailed information on patterns of former smoking. We are

not able to disentangle effects of air pollution on lung cancer risk between former heavy versus former light smokers, which might be expected to differ. Homogeneity tests did not provide support for different effects by smoking subgroups.

A recent study (Silverman et al. 2012) in a large cohort of US non-metal miners reported a dose-response curve that was steeper at lower exposures to respirable elemental carbon, a marker for diesel exhaust, and levelled off at higher exposures. In this study, reduced diesel exhaust-associated lung cancer risk was observed among heavy smokers. This pattern is similar to our observation of a smaller lung cancer risk associated with PM for current smokers. The authors propose a number of biological mechanisms to explain this effect; these include decreased lung deposition of diesel exhaust among smokers and polycyclic aromatic hydrocarbons, present in smoking, diesel exhaust, and $PM_{2.5}$, competing for metabolic activation, among others. However, the exact mechanism leading to this reduced risk among smokers is still unclear. Thus, more careful consideration of potential interaction between PM and smoking for lung cancer and other diseases seems warranted; large, robust data sets will be needed for this work.

The original risk estimates included in our analyses assume a log-linear relation between PM exposure and lung cancer rates. Thus, the data available for this meta-analysis do not provide the opportunity to further evaluate this assumption. However, alternatives to a linear exposure-response model have been considered in analyses of data from the ACS (Pope et al. 2002; Turner et al. 2011), Harvard Six Cities (Lepeule et al. 2012), Canadian National Enhanced Cancer Surveillance System (Hystad et al. 2013), Rome Longitudinal (Cesaroni et al. 2013), NHS (Puett et al., in press), and ESCAPE (Raaschou-Nielsen et al. 2013) studies, which included categorical modelling and application of smoothing functions. All of these analyses concluded that there is no evidence of marked deviation from linearity. Pope et al. (2011) also reported a near linear

relation of lung cancer risk with estimated daily $PM_{2.5}$ dose in an analysis that integrated information on lung cancer risk associated findings of risk from diverse combustion sources (Pope et al. 2011).

Conclusion

The results of these analyses, and the decision of the IARC working group to classify outdoor air pollution as a Group 1 carcinogen, further justify efforts to reduce exposures to air pollutants that can arise from many sources. The Global Burden of Disease collaboration estimated that approximately 3.22 million deaths were caused by exposure to air pollution in 2010, an increase from 2.91 million deaths attributed to air pollution in 1990 (Lim et al. 2012). Cancers of the trachea, bronchus, or lung represent approximately 7% of total mortality attributable to $PM_{2.5}$ in 2010. The results of the meta-analysis provided here could be useful for better quantifying the burden of lung cancer associated with air pollution. The Group I classification raises questions regarding individual components in the air pollution mixture, such as the carcinogenic potential of each component as well as through what pathways they may contribute to cancer risk.

References

Beelen R, Hoek G, van den Brandt PA, Goldbohm RA, Fischer P, Schouten LJ, et al. 2008. Long-term effects of traffic-related air pollution on mortality in a dutch cohort (nlcs-air study). Environ Health Perspect 116:196-202.

Beeson WL, Abbey DE, Knutsen SF. 1998. Long-term concentrations of ambient air pollutants and incident lung cancer in california adults: Results from the ahsmog study.Adventist health study on smog. Environ Health Perspect 106:813-822.

Brauer M, Avila-Casado C, Fortoul TI, Vedal S, Stevens B, Churg A. 2001. Air pollution and retained particles in the lung. Environ Health Perspect 109:1039-1043.

Brauer M, Amann M, Burnett RT, Cohen A, Dentener F, Ezzati M, et al. 2012. Exposure assessment for estimation of the global burden of disease attributable to outdoor air pollution. Environmental Science & Technology 46:652-660.

Buschini A, Cassoni F, Anceschi E, Pasini L, Poli P, Rossi C. 2001. Urban airborne particulate: Genotoxicity evaluation of different size fractions by mutagenesis tests on microorganisms and comet assay. Chemosphere 44:1723-1736.

Cao J, Yang CX, Li JX, Chen RJ, Chen BH, Gu DF, et al. 2011. Association between long-term exposure to outdoor air pollution and mortality in china: A cohort study (vol 186, pg 1594, 2011). Journal of Hazardous Materials 191:398-398.

Carey IM, Atkinson RW, Kent AJ, van Staa T, Cook DG, Anderson HR. 2013. Mortality associations with long-term exposure to outdoor air pollution in a national english cohort. Am J Respir Crit Care Med 187:1226-1233.

Cesaroni G, Badaloni C, Gariazzo C, Stafoggia M, Sozzi R, Davoli M, et al. 2013. Long-term exposure to urban air pollution and mortality in a cohort of more than a million adults in rome. Environmental Health Perspectives 121:324-331.

DerSimonian R, Laird N. 1986. Meta-analysis in clinical trials. Control Clin Trials 7:177-188.

Duval S, Tweedie R. 2000. A nonparametric "trim and fill" method of accounting for publication bias in meta-analysis. Journal of the American Statistical Association 95:89-98.

Egger M, Schneider M, Davey Smith G. 1998. Spurious precision? Meta-analysis of observational studies. BMJ 316:140-144.

Hales S, Blakely T, Woodward A. 2012. Air pollution and mortality in new zealand: Cohort study. J Epidemiol Community Health 66:468-473.

Hart JE, Garshick E, Dockery DW, Smith TJ, Ryan L, Laden F. 2011. Long-term ambient multipollutant exposures and mortality. Am J Respir Crit Care Med 183:73-78.

Heinrich J, Thiering E, Rzehak P, Kramer U, Hochadel M, Rauchfuss KM, et al. 2013. Long-term exposure to no2 and pm10 and all-cause and cause-specific mortality in a prospective cohort of women. Occupational and Environmental Medicine 70:179-186.

Higgins JP, Thompson SG, Deeks JJ, Altman DG. 2003. Measuring inconsistency in meta-analyses. BMJ 327:557-560.

Higgins JPT, Green S, Cochrane Collaboration. 2008. Cochrane handbook for systematic reviews of interventions. Chichester, England ; Hoboken, NJ:Wiley-Blackwell.

Howlader N, Noone A, Krapcho M, Garshell J, Neyman N, Altekruse S, et al. 2013. Seer cancer statistics review, 1975-2010. National Cancer Institute Bethesda, MD.

Hystad P, Demers PA, Johnson KC, Carpiano RM, Brauer M. 2013. Long-term residential exposure to air pollution and lung cancer risk. Epidemiology 24:762-772.

IARC. In press. Monographs on the evaluation of carcinogenic risks to humans: Outdoor air pollution. Lyon, France:International Agency for Research on Cancer.

Jerrett M, Burnett RT, Beckerman BS, Turner MC, Krewski D, Thurston G, et al. 2013. Spatial analysis of air pollution and mortality in california. Am J Respir Crit Care Med 188:593-599.

Katanoda K, Sobue T, Satoh H, Tajima K, Suzuki T, Nakatsuka H, et al. 2011. An association between long-term exposure to ambient air pollution and mortality from lung cancer and respiratory diseases in japan. J Epidemiol 21:132-143.

Krewski D JM, Burnett RT, Ma R, Hughes E, Shi Y, Turner MC, Pope CA, 3rd, Thurston G, Calle EE, et al. 2009. Extended follow-up and spatial analysis of the american

cancer society study linking particulate air pollution and mortality. Res Rep Health Eff Inst:5-114; discussion 115-136.

Lepeule J, Laden F, Dockery D, Schwartz J. 2012. Chronic exposure to fine particles and mortality: An extended follow-up of the harvard six cities study from 1974 to 2009. Environ Health Perspect 120:965-970.

Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, et al. 2012. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: A systematic analysis for the global burden of disease study 2010. Lancet 380:2224-2260.

Lipsett MJ, Ostro BD, Reynolds P, Goldberg D, Hertz A, Jerrett M, et al. 2011. Long-term exposure to air pollution and cardiorespiratory disease in the california teachers study cohort. Am J Respir Crit Care Med 184:828-835.

Loomis D, Grosse Y, Lauby-Secretan B, Ghissassi FE, Bouvard V, Benbrahim-Tallaa L, et al. 2013. The carcinogenicity of outdoor air pollution. The Lancet Oncology.

McDonnell WF, Nishino-Ishikawa N, Petersen FF, Chen LH, Abbey DE. 2000. Relationships of mortality with the fine and coarse fractions of long-term ambient pm10 concentrations in nonsmokers. J Expo Anal Environ Epidemiol 10:427-436.

Naess O, Nafstad P, Aamodt G, Claussen B, Rosland P. 2007. Relation between concentration of air pollution and cause-specific mortality: Four-year exposures to nitrogen dioxide and particulate matter pollutants in 470 neighborhoods in oslo, norway. Am J Epidemiol 165:435-443.

Pope CA, 3rd, Burnett RT, Thun MJ, Calle EE, Krewski D, Ito K, et al. 2002. Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. JAMA 287:1132-1141.

Pope CA, 3rd, Burnett RT, Turner MC, Cohen A, Krewski D, Jerrett M, et al. 2011. Lung cancer and cardiovascular disease mortality associated with ambient air pollution and cigarette smoke: Shape of the exposure-response relationships. Environ Health Perspect 119:1616-1621.

Puett R, Hart J, Yanosky J, Spiegelman D, Wang M, Fisher J, et al. In press. Lung cancer, particulate matter and traffic-related air pollution exposures in the nurses' health study cohort. Environ Health Perspect.

Raaschou-Nielsen O, Andersen ZJ, Beelen R, Samoli E, Stafoggia M, Weinmayr G, et al. 2013. Air pollution and lung cancer incidence in 17 european cohorts: Prospective analyses from the european study of cohorts for air pollution effects (escape). Lancet Oncology 14:813-822.

Samet J, Cohen. A. 2006. Air pollution. In: Cancer epidemiology and prevention, Part 3rd (Schottenfeld D, Fraumeni JF, eds). Oxford ; New York:Oxford University Press, 355-376.

Silverman DT, Samanic CM, Lubin JH, Blair AE, Stewart PA, Vermeulen R, et al. 2012. The diesel exhaust in miners study: A nested case-control study of lung cancer and diesel exhaust. J Natl Cancer Inst 104:855-868.

Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, et al. 2011. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ 343:d4002.

Stuart BO. 1976. Deposition and clearance of inhaled particles. Environ Health Perspect 16:41-53.

Turner MC, Krewski D, Pope CA, 3rd, Chen Y, Gapstur SM, Thun MJ. 2011. Long-term ambient fine particulate matter air pollution and lung cancer in a large cohort of never-smokers. Am J Respir Crit Care Med 184:1374-1381.

Valavanidis A, Fiotakis K, Vlachogianni T. 2008. Airborne particulate matter and human health: Toxicological assessment and importance of size and composition of particles for oxidative damage and carcinogenic mechanisms. J Environ Sci Health C Environ Carcinog Ecotoxicol Rev 26:339-362.

Table 1. Summary of studies included in meta-analyses of lung cancer risk associated with exposure to particulate matter.

Continent	ID	Source	Number of events (mortality or incidence)	Total population	Study period	Exposure assessment method	Exposure distribution: mean ± SD	Study title
North America								
California, USA	01	Beeson et al. 1998	16 (incidence)	6,338	1977 - 1992	Fixed Site Monitor	PM_{10}: 51.0 ± 16.5	Adventist Health Study on Smog (AHSMOG)
California, USA	02	McDonnell et al. 2000	13 (mortality)	3,769	1977 - 1992	Fixed Site Monitor	$PM_{2.5}$: 31.9 ± 10.7	Adventist Health Study on Smog (AHSMOG)
United States	03	Pope et al. 2002	n/a	415,000	1982 - 1998	Fixed Site Monitor	PM_{10}: 28.8 ± 5.9	American Cancer Society Cancer Prevention Study II
United States	04	Krewski et al. 2009	16,615 (mortality)	499, 968	1982 - 2000	Fixed Site Monitor	$PM_{2.5}$: 21.2 ± 10.8 (1979-1983) $PM_{2.5}$: 14.0 ± 9.1 (1999-2000)	American Cancer Society Cancer Prevention Study II
Los Angeles, CA, United States	05	Jerrett et al. 2013	1,481 (mortality)	73,711	1982 - 2000	Land use regression	$PM_{2.5}$: 14.1 ± 12.4	American Cancer Society Cancer Prevention Study II
United States	06	Hart et al. 2011	800 (mortality)	53,814	1985 - 2000	Inverse distance weighting ($PM_{2.5}$) /spatio-temporal (PM_{10})	$PM_{2.5}$: 14.1 ± 4.0 PM_{10}: 26.8 ± 6.0	Trucking Industry Particle Study (TrIPS)
California, USA	07	Lipsett et al. 2011	275 (PM_{10}), 234 ($PM_{2.5}$) (mortality)	101,784 (PM_{10}), 73,489 ($PM_{2.5}$)	1997 - 2005	Inverse distance weighting	$PM_{2.5}$: 15.6 ± 4.5 PM_{10}: 29.2 ± 9.8	California Teachers Study
United States	08	Lepeule et al. 2012	632 (mortality)	8,096	1975 - 2009	Fixed Site Monitor	$PM_{2.5}$: 15.9 [b]	Harvard Six Cities Study
Canada	09	Hystad et al. 2013	2,390 (incidence)	5,897	1994 - 1997	Spatio-temporal model	$PM_{2.5}$: 11.9 ± 3.0	National Enhanced Cancer Surveillance System Case-Control study
United States	10	Puett et al. 2013	1,648 (incidence)	97,865	1998-2010	Spatio-temporal model	$PM_{2.5}$: 13.1 ± 3.0 PM_{10}: 21.6 ± 6.0	Nurses' Health Study
Europe								
Netherlands	11	Beelen et al., 2008	1,888 (mortality)	120,852	1986 - 1997	Land use regression	$PM_{2.5}$: 28.3 ± 2.1	Netherlands Cohort study of Diet and Cancer.
United Kingdom	12	Carey et al. 2013	5,273 (mortality)	830,842	2003 - 2007	Air dispersion	$PM_{2.5}$: 12.9 ± 1.4 PM_{10}: 19.7 ± 2.3	Clinical Practice Research Datalink

Continent	ID	Source	Number of events (mortality or incidence)	Total population	Study period	Exposure assessment method	Exposure distribution: mean ± SD	Study title
Italy	13	Cesaroni et al. 2013	12,208 (mortality)	1,265,058	2001 - 2010	Air dispersion	$PM_{2.5}$: 23.0 ± 4.4	Rome Longitudinal Study
Germany	14	Heinreich et al. 2013	41 (mortality)	4,752	1980 - 2008	Fixed Site Monitor	PM_{10}: 43.7 [b]	German Women's Health Study
European Union	15	Raaschou-Neilsen et al 2013	2,095 (incidence)	312,944	1990's*	Land use regression	$PM_{2.5}$: 13.4 ± 1.2 PM_{10}: 21.3 ± 2.7	European Study of Cohorts for Air Pollution Effects (ESCAPE)
Other								
China	16	Cao et al. 2011	624 (mortality)	70,947	1991 - 2000	Fixed Site Monitor	$PM_{2.5}$: [a]	China National Hypertension follow-up survey
Japan	17	Katanoda et al. 2011	421 (mortality)	63,520	1983 - 1995	Fixed Site Monitor	$PM_{2.5}$: 28.8 [b]	Three Prefecture Cohort Study
New Zealand	18	Hales et al. 2012	1,686 (mortality)	1,050,222	1996 - 1999	Land use regression	PM_{10}: 8.3 ± 8.4	New Zealand Census Mortality Study

[a]Mean and standard deviation of $PM_{2.5}$ for Cao et al. 2011 could not be obtained. The numbers reported represent the range of exposure estimated by converting TSP to $PM_{2.5}$ with a 3:1 ratio. [b]Standard deviation not reported.

Table 2. Estimates for the relationship between a 10 μg/m^3 change in $PM_{2.5}$ and PM_{10} exposure and lung cancer risk.

Exposure	RR (95% CI)	I-squared (p-value)	Homogeneity test[a]	Study ID numbers[b]
$PM_{2.5}$				
Full meta estimate	1.09 (1.04, 1.14)	56.4% (0.007)		All
Continent				
North America	1.11 (1.05, 1.16)	6.5% (0.378)		2, 4, 5, 6, 7, 8, 9, 10
Europe	1.03 (0.89, 1.20)	50.0% (0.112)		11, 12, 13, 15
Others	1.13 (0.94, 1.34)	91.0% (0.001)	p = 0.656	16, 17
Exposure assessment method				
Fixed site monitor	1.12 (1.04, 1.21)	77.1% (0.002)		2, 4, 8, 16, 17
Other	1.06 (1.00, 1.13)	16.2% (0.298)	p = 0.268	5, 6, 7, 9, 10, 11, 12, 13, 15
Smoking status				
Never	1.18 (1.00, 1.39)	0.0% (0.928)		3, 7, 8, 9, 10, 15
Former	1.44 (1.04, 2.01)	66.3% (0.031)		3, 8, 9, 15
Current	1.06 (0.97, 1.15)	0.0% (0.544)	p = 0.197	3, 8, 9, 15
Confounder adjustment				
Smoking status	1.10 (1.04, 1.17)	61.4% (0.004)		2, 4, 7, 8, 9, 10, 11, 12, 15, 16, 17
SES/income	1.04 (0.96, 1.12)	24.2% (0.252)		5, 7, 10, 11, 13, 15
Education	1.07 (1.03, 1.11)	37.7% (0.117)		4, 8, 9, 10, 12, 13, 15, 16,
Occupation	1.08 (1.05, 1.11)	0.4% (0.420)		4, 6, 7, 9, 10, 13, 15
PM_{10}				
Full meta estimate	1.08 (1.00, 1.17)	74.6% (>0.001)		All
Continent				
North America	1.02 (0.96, 1.09)	57.7% (0.051)		1, 3, 6, 7, 10
Europe	1.27 (0.96, 1.68)	76.5% (0.014)		12, 14, 15
Others	1.16 (1.04, 1.29)	--	p = 0.074	18
Exposure assessment method				
Fixed site monitor				
Other	1.17 (0.93, 1.47)	87.3% (>0.000)		1, 3, 14
Smoking status	1.07 (0.99, 1.15)	43.9% (0.113)	p = 0.484	6, 7, 10, 12, 15, 18
Never				
Former	1.11 (0.94, 1.33)	0.0% (0.407)		7, 10, 15
Current	--	--		--

Exposure	RR (95% CI)	I-squared (p-value)	Homogeneity test[a]	Study ID numbers[b]
Confounder adjustment				
Smoking status	1.08 (0.99, 1.17)	77.2% (>0.001)		1, 3, 7, 10, 12, 14, 15, 18
SES/income	1.08 (0.97, 1.20)	65.5% (0.033)		7, 10, 15, 18
Education	1.11 (1.01, 1.21)	79.7% (>0.001)		1, 3, 10, 12, 14, 15, 18
Occupation	1.02 (0.95, 1.10)	56.7% (0.055)		3, 6, 7, 10, 15

Estimates are the result of random effects meta-analysis.

[a]p-value based on a chi-square distribution. [b]Studies included in the analysis according to ID numbers listed in Table 1.

Results from Naess et al. (2007) could not be converted to 10 $\mu g/m^3$ units, and are, thus, excluded. The change in lung cancer mortality associated with a 1-quartile increase in $PM_{2.5}$ and PM_{10} were identical, 1.26 (95% CI: 1.23, 1.28).

Table 3. Estimates for the relationship between a 10 μg/m^3 change in $PM_{2.5}$ and PM_{10} and histological cancer subtypes.

Exposure and outcome	RR (95% CI)	N*	Studies included (by ID)[b]
$PM_{2.5}$			
Adenocarcinoma	1.40 (1.07, 1.83)	2,339	9, 10, 15
Squamous cell carcinoma	1.11 (0.72, 1.72)	1,523	9, 15
PM_{10}			
Adenocarcinoma	1.29 (1.02, 1.63)	965	10, 15
Squamous cell carcinoma	--	--	--

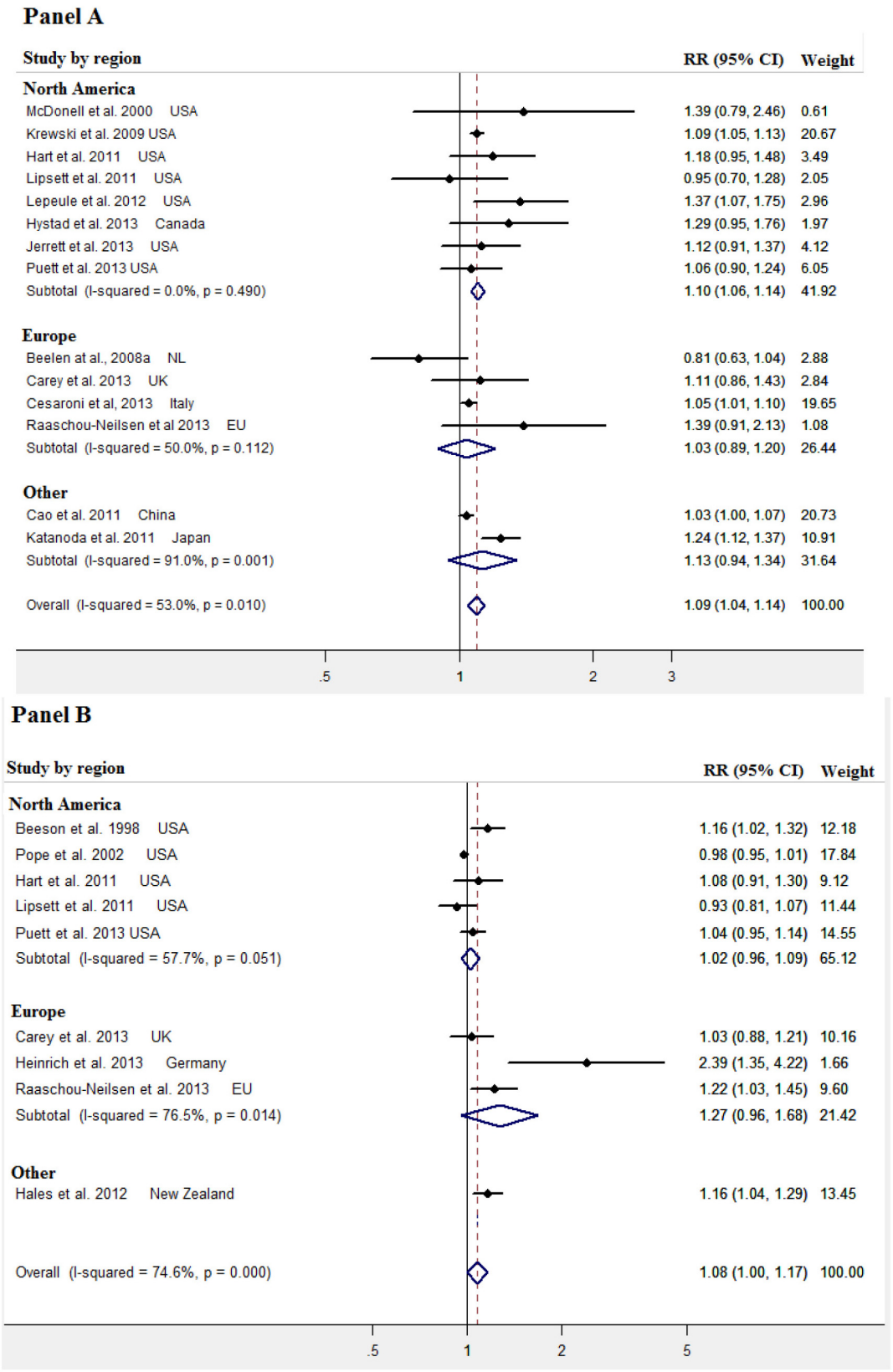
Estimates are the result of random effects meta-analysis.

[b]Studies included in the analysis according to ID numbers listed in Table 1.

Figure legend

Figure 1. Estimates of lung cancer risk associated a 10 $\mu g/m^3$ change in exposure to $PM_{2.5}$ (a) and PM_{10} (b) exposure overall and by geographic region of study. Note: Jerrett et al. (2013) contributes neither to the overall nor to the continent specific meta estimates; it is only included here for visualization. Weights represent the contribution of each study effect estimate to the overall meta-estimate.

Figure 1.


Panel A
Study by region
RR (95% CI)
Weight
North America
McDonell et al. 2000 USA
1.39 (0.79, 2.46) 0.61
Krewski et al. 2009 USA
1.09 (1.05, 1.13) 20.67
Hart et al. 2011 USA
1.18 (0.95, 1.48) 3.49
Lipsett et al. 2011 USA
0.95 (0.70, 1.28) 2.05
Lepeule et al. 2012 USA
1.37 (1.07, 1.75) 2.96
Hystad et al. 2013 Canada
1.29 (0.95, 1.76) 1.97
Jerrett et al. 2013 USA
1.12 (0.91, 1.37) 4.12
Puett et al. 2013 USA
1.06 (0.90, 1.24) 6.05
Subtotal (I-squared = 0.0%, p = 0.490)
1.10 (1.06, 1.14) 41.92
Europe
Beelen at al., 2008a NL
0.81 (0.63, 1.04) 2.88
Carey et al. 2013 UK
1.11 (0.86, 1.43) 2.84
Cesaroni et al, 2013 Italy
1.05 (1.01, 1.10) 19.65
Raaschou-Neilsen et al 2013 EU
1.39 (0.91, 2.13) 1.08
Subtotal (I-squared = 50.0%, p = 0.112)
1.03 (0.89, 1.20) 26.44
Other
Cao et al. 2011 China
1.03 (1.00, 1.07) 20.73
Katanoda et al. 2011 Japan
1.24 (1.12, 1.37) 10.91
Subtotal (I-squared = 91.0%, p = 0.001)
1.13 (0.94, 1.34) 31.64
Overall (I-squared = 53.0%, p = 0.010)
1.09 (1.04, 1.14) 100.00
.5
1
2
3
Panel B
Study by region
RR (95% CI)
Weight
North America
Beeson et al. 1998 USA
1.16 (1.02, 1.32) 12.18
Pope et al. 2002 USA
0.98 (0.95, 1.01) 17.84
Hart et al. 2011 USA
1.08 (0.91, 1.30) 9.12
Lipsett et al. 2011 USA
0.93 (0.81, 1.07) 11.44
Puett et al. 2013 USA
1.04 (0.95, 1.14) 14.55
Subtotal (I-squared = 57.7%, p = 0.051)
1.02 (0.96, 1.09) 65.12
Europe
Carey et al. 2013 UK
1.03 (0.88, 1.21) 10.16
Heinrich et al. 2013 Germany
2.39 (1.35, 4.22) 1.66
Raaschou-Neilsen et al. 2013 EU
1.22 (1.03, 1.45) 9.60
Subtotal (I-squared = 76.5%, p = 0.014)
1.27 (0.96, 1.68) 21.42
Other
Hales et al. 2012 New Zealand
1.16 (1.04, 1.29) 13.45
Overall (I-squared = 74.6%, p = 0.000)
1.08 (1.00, 1.17) 100.00
.5
1
2
5